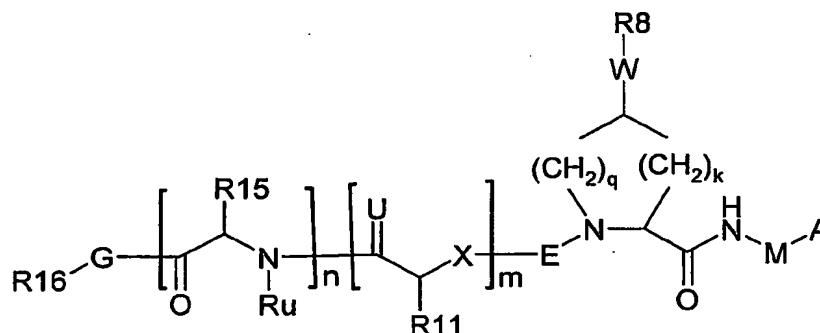


Claims

1. A compound of the formula I:



5 wherein

A is $C(=OO)R^1$, $C(=O)NHSO_2R^2$, $C(=O)NHR^3$, or $CR^4R^{4'}$ wherein;

R^1 is hydrogen, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl;

R^2 is C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl;

R^3 is C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl, $-OC_1$ - C_6 alkyl, $-OC_0$ - C_3 alkylcarbocyclyl, $-OC_0$ - C_3 alkylheterocyclyl;

R^4 is $=O$, halo, amino, or OH ; or R^4 and $R^{4'}$ together are $=O$;

$R^{4'}$ is C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl; wherein

R^2 , R^3 , and $R^{4'}$ are each optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl, NH_2CO- , $Y-NRaRb$, $Y-O-Rb$, $Y-C(=O)Rb$, $Y-(C=O)NRaRb$, $Y-NRaC(=O)Rb$, $Y-NHSO_pRb$, $Y-S(=O)_pRb$ and $Y-S(=O)_pNRaRb$, $Y-C(=O)ORb$, $Y-NRaC(=O)ORb$;

Y is independently a bond or C_1 - C_3 alkylene;

Ra is independently H or C_1 - C_3 alkyl;

Rb is independently H, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl or C_0 - C_3 alkylheterocyclyl;

p is independently 1 or 2;

M is $CR^7R^{7'}$ or NRu ;

R^7 is C_1 - C_6 alkyl, C_0 - C_3 alkyl/ C_3 - C_7 cycloalkyl, or C_2 - C_6 alkenyl, any of which is optionally substituted with 1-3 halo atoms, or an amino, -SH, or C_0 - C_3 alkylcycloalkyl group; or R^7 is J;

R^7 is H or taken together with R^7 forms a C_3 - C_6 cycloalkyl ring optionally substituted with R^{7a} wherein;

R^{7a} is C_1 - C_6 alkyl, C_3 - C_5 cycloalkyl, C_2 - C_6 alkenyl any of which may be optionally substituted with halo; or R^{7a} can be J;

q is 0 to 3 and k is 0 to 3; where $q+k \geq 1$;

W is $-CH_2-$, $-O-$, $-OC(=O)H-$, $-OC(=O)-$, $-S-$, $-NH-$, $-NRa$, $-NHSO_2-$, $-NHC(=O)NH-$ or $-NHC(=O)-$, $-NHC(=S)NH-$ or a bond;

R^8 is a ring system containing 1 or 2 saturated, partially saturated or unsaturated rings each of which has 4-7 ring atoms and each of which has 0 to 4 hetero atoms independently selected from S, O and N, the ring system being optionally spaced from W by a C_1 - C_3 alkylene group; or R^8 is C_1 - C_6 alkyl; any of which R^8 groups can be optionally mono-, di-, or tri-substituted with R^9 , wherein

R^9 is independently selected from the group consisting of halo, oxo, nitrile, azido, nitro, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl, $NH_2C(=O)-$, $Y-NRaRb$, $Y-O-Rb$, $Y-C(=O)Rb$, $Y-(C=O)NRaRb$, $Y-NRaC(=O)Rb$, $Y-NHSO_pRb$, $Y-S(=O)_pRb$, $Y-S(=O)_pNRaRb$, $Y-C(=O)ORb$, $Y-NRaC(=O)ORb$; wherein said carbocyclyl or heterocyclyl is optionally substituted with R^{10} ;

wherein

R^{10} is C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, amino, amido, sulfonyl, (C_1 - C_3 alkyl)sulfonyl, NO_2 , OH, SH, halo, haloalkyl, carboxyl;

E is $-C(=O)-$, $-C(=S)-$, $-S(=O)_2-$, $-S(=O)-$, $-C(=N-Rf)-$;

Rf is H, $-CN$, $-C(=O)NRaRb$; $-C(=O)C_1$ - C_3 alkyl;

X is $-NRx-$ where Rx is H, C_1 - C_5 alkyl or J; or in the case where E is $-C(=O)-$, X can also be $-O-$ or $-NRjNRj-$;

wherein one of Rj is H and the other is H, C_1 - C_5 alkyl or J;

R^{11} is H, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1 - C_6 alkyl, C_0 - C_3 alkylcarbocyclyl, C_0 - C_3 alkylheterocyclyl, $NH_2C(=O)-$, $Y-NRaRb$, $Y-O-Rb$, $Y-C(=O)Rb$, $Y-(C=O)NRaRb$,

Y-NRaC(=O)Rb, Y-NHSO_pRb, Y-S(=O)_pRb, Y-S(=O)_pNRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb; or R¹¹ is J;

J, if present, is a single 3 to 10-membered saturated or partially unsaturated alkylene chain extending from the R⁷/R^{7'} cycloalkyl or from the carbon atom to which R⁷ is attached to one of R_j, R_x, R_y or R¹¹ to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -NR¹²-, and wherein 0 to 3 carbon atoms in the chain are optionally substituted with R¹⁴; wherein;

R¹² is H, C₁-C₆alkyl, C₃-C₆cycloalkyl, or C(=O)R¹³;

R¹³ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl;

R¹⁴ is independently selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, hydroxy, halo, amino, oxo, thio and C₁-C₆thioalkyl;

Ru is independently H or C₁-C₃alkyl;

m is 0 or 1; n is 0 or 1;

U is =O or is absent;

R¹⁵ is H, C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C₁-C₆alkyl, C₀-C₃alkylheterocyclyl, C₀-C₃alkylcarbocyclyl, NH₂CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO_pRb, Y-S(=O)_pRb, Y-S(=O)_pNRaRb, Y-C(=O)ORb, Y-

NRaC(=O)ORb;

G is -O-, -NRY-, -NR_jNR_j-: where one R_j is H and the other R_j is H, C₁-C₅alkyl or J; R_y is H, C₁-C₃alkyl; or R_y is J;

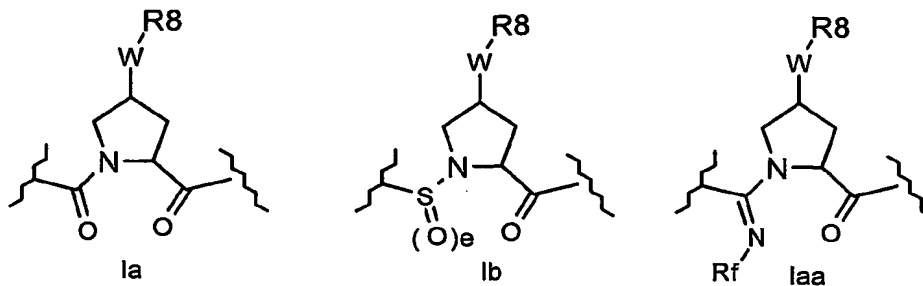
R¹⁶ is H; or C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C₁-C₆alkyl, C₀-

C₃alkylcarbocyclyl, C₀-C₃alkylheterocyclyl, NH₂CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO_pRb, Y-S(=O)_pRb, Y-S(=O)_pNRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

with the proviso that when m=n=0 and G is O then R¹⁶ is not tert.butyl or phenyl; or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1, wherein M is CR⁷R^{7'}.

3. A compound according to claim 1, with the partial structure Ia, Ib or laa:



where e is 1 or 2.

5

4. A compound to claim 1, wherein E is -C(=O)-.

5. A compound according to claim 1, wherein m is 0 and n is 0.

- 10 6. A compound according to claim 5, wherein G is -NR_y- or -NR_jNR_j-.

7. A compound according to claim 6, where R_y or one of the R_j groups is J, thereby defining a macrocyclic compound.

- 15 8. A compound according to claim 7, wherein R¹⁶ is H, C₁-C₃ alkyl or C₃-C₆ cycloalkyl.

9. A compound according to claim 1, wherein m is 1.

- 20 10. A compound according to claim 9, wherein X is -NR_x-.

11. A compound according to claim 9, wherein U is O.

12. A compound according to claim 9, wherein R¹¹ is C₁-C₆alkyl, C₀-C₃alkylcarbocyclyl, C₀-C₃alkylaryl or C₀-C₃alkylheteroaryl, any of which is optionally
- 25

substituted with halo, amino, C₁-C₆alkoxy, C₁-C₆thioalkyl, carboxyl, (C₁-C₆alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl, and especially wherein the substituent is hydroxy or C(=O)OR¹⁴.

- 5 13. A compound according to claim 12, wherein R¹¹ is phenylethyl, 2,2-dimethyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl; or especially tert-butyl, iso-butyl, or cyclohexyl.
14. A compound according to claim 9, wherein one of Rx or R¹¹ is J, thereby
10 defining a macrocyclic compound.
15. A compound according to claim 9, wherein n is 1.
16. A compound according to claim 15, wherein R¹⁵ is C₁-C₆alkyl or C₀-
15 C₃alkylcarbocyclyl, either of which is optionally substituted.
17. A compound according to claim 16, wherein R¹⁵ is cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.
- 20 18. A compound according to claim 9, wherein G is NR_y or -NR_jNR_j-, where R_y or one R_j is H or methyl, and the other R_j is H.
19. A compound according to claim 18, wherein R¹⁶ is H, C₁-C₆alkyl, or a 5 or 6
25 membered heterocycle, especially morpholine, piperidine or piperazine.
20. A compound according to claim 9, wherein R¹⁶ is C₁-C₆alkyl, C₀-C₃alkylheterocyclyl, C₀-C₃alkylcarbocyclyl, any of which is optionally substituted with hydroxy, halo, amino, or C₁-C₆alkoxy.
- 30 21. A compound according to claim 20, wherein R¹⁶ is 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-

methylenedioxybenzyl, cyclohexyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

22. A compound according to claim 1, wherein W is -OC(=O)-, -NRa-, -NHS(O)₂- or
5 -NHC(=O)-; or especially -OC(=O)NH- or -NH.

23. A compound according to claim 1, wherein W is -S-, a bond or especially -O-.

24. A compound according to claim 22 or 23 wherein R⁸ is optionally substituted
10 C₀-C₃alkylcarbocyclyl or optionally substituted C₀-C₃-alkylheterocyclyl.

25. A compound according to claim 24, wherein the C₀-C₃ alkyl moiety is
methylene or preferably a bond.

15 26 A compound according to claim 25 wherein R⁸ is C₀-C₃alkylaryl, or C₀-
C₃alkylheteroaryl, either of which is optionally mono, di, or tri substituted with R⁹,
wherein;

R⁹ is C₁-C₆ alkyl, C₁-C₆alkoxy, NO₂, OH, halo, trifluoromethyl, amino amido
optionally mono- or di-substituted with C₁-C₆alkyl, C₀-C₃alkylaryl, C₀-
20 C₃alkylheteroaryl, carboxyl, aryl or heteroaryl being optionally substituted with
R¹⁰; wherein

R¹⁰ is C₁-C₆alkyl, C₃-C₇cycloalkyl, C₁-C₆alkoxy, amino optionally mono- or
di-substituted with C₁-C₆alkyl, amido, sulfonylC₁-C₃alkyl, NO₂, OH, halo,
trifluoromethyl, carboxyl, or heteroaryl.

25

27 A compound according to claim 26 wherein R⁹ is C₁-C₆ alkyl, C₁-C₆alkoxy,
amino, di-(C₁-C₃ alkyl)amino, C₁-C₃alkylamide, aryl or heteroaryl, the aryl or
heteroaryl being optionally substituted with R¹⁰; wherein

R¹⁰ is C₁-C₆alkyl, C₃-C₇cycloalkyl, C₁-C₆alkoxy, amino, mono- or di-C₁-C₃
30 alkylamino, amido, halo, trifluoromethyl, or heteroaryl.

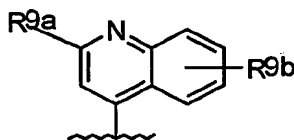
28. A compound according to claim 27, wherein, R^{10} is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, amino optionally mono- or di substituted with C_1 - C_3 alkyl, amido, C_1 - C_3 -alkylamide, halo, or heteroaryl.

5 29. A compound according to claim 28 wherein R^{10} is methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with C_1 - C_3 alkyl, amido, or C_1 - C_3 alkyl thiazolyl.

30 A compound according to claim 29, wherein R^8 is 1-naphthylmethyl, 2-naphthylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyll any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

31 A compound according to claim 30 wherein R^8 is 1-naphthylmethyl, or quinolinyll any of which is unsubstituted, mono, or disubstituted with R^9 as defined.

32 A compound according to claim 31 wherein R^8 is:



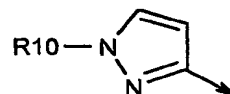
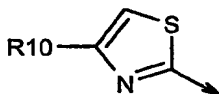
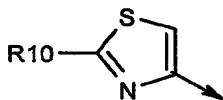
wherein R^{9a} is C_1 - C_6 alkyl; C_1 - C_6 alkoxy; thio C_1 - C_3 alkyl; amino optionally substituted with C_1 - C_6 alkyl; C_0 - C_3 alkylaryl; or C_0 - C_3 alkylheteroaryl, C_0 - C_3 alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with R^{10} wherein

R^{10} is C_1 - C_6 alkyl, C_0 - C_3 alkyl C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, amino optionally mono- or di-substituted with C_1 - C_6 alkyl, amido, C_1 - C_3 alkyl amide; and

R^{9b} is C_1 - C_6 alkyl, C_1 - C_6 -alkoxy, amino, di(C_1 - C_3 alkyl)amino, (C_1 - C_3 alkyl) amide, NO_2 , OH, halo, trifluoromethyl, carboxyl.

33 A compound according to claim 32, wherein R^{9a} is aryl or heteroaryl, either of which is optionally substituted with R^{10} as defined.

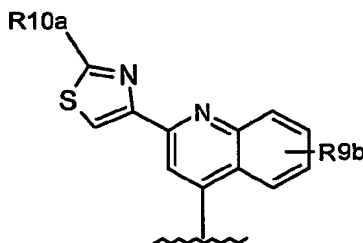
34 A compound according to 33, wherein R^{9a} is selected from the group consisted of:



wherein R¹⁰ is H, C₁-C₆alkyl, or C₀-C₃alkylcycloalkyl, amino optionally mono- or disubstituted with C₁-C₆alkyl, amido, (C₁-C₃alkyl)amide.

35. A compound according to claim 33, wherein R^{9a} is optionally substituted phenyl, preferably phenyl substituted with C₁-C₆alkyl; C₁-C₆alkoxy; or halo.

36. A compound according to claim 32, wherein R⁸ is:



wherein R^{10a} is H, C₁-C₆alkyl, or C₀-C₃alkylcarbocyclyl, amino optionally mono- or disubstituted with C₁-C₆alkyl, amido, heteroaryl or heterocyclyl; and R^{9b} is C₁-C₆ alkyl, C₁-C₆-alkoxy, amino, di(C₁-C₃ alkyl)amino, amido, NO₂, OH, halo, trifluoromethyl, or carboxyl.

37. A compound according to any claim 32, wherein R^{9b} is C₁-C₆-alkoxy, preferably methoxy.

38. A compound according to claim 1, wherein A is $C(=O)NHSO_2R^2$.

39. A compound according to claim 38, wherein R² is optionally substituted C₁-C₆ alkyl, preferably methyl.

40. A compound according to claim 38, wherein R^2 is optionally substituted C_3 - C_7 cycloalkyl, preferably cyclopropyl.

41. A compound according to claim 38, wherein R^2 is optionally substituted C_0 - C_6 alkylaryl, preferably optionally substituted phenyl.

42. A compound according to claim 1, wherein A is $C(=O)OR^1$.

43. A compound according to claim 42, wherein R^1 is H or C_1 - C_6 alkyl, preferably hydrogen, methyl, ethyl, or tert-butyl.

44. A compound according to claim 2, wherein R^7 is H and R^7 is n-ethyl, cyclopropylmethyl, cyclopropyl, cyclobutylmethyl cyclobutyl or mercaptomethyl, preferably n-propyl or 2,2-difluoroethyl.

45. A compound according to claim 2, wherein R^7 and R^7 together define a spiro-cyclopropyl or spiro-cyclobutyl ring, both optionally mono or di-substituted with R^{7a} wherein;

R^{7a} is C_1 - C_6 alkyl, C_3 - C_5 cycloalkyl, or C_2 - C_6 alkenyl, any of which is optionally substituted with halo; or R^{7a} is J.

46. A compound according to claim 45 wherein the ring is a spiro-cyclopropyl ring substituted with R^{7a} wherein;

R^{7a} is ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl.

47. A compound according to claim 2, wherein R^7 is J and R^7 is H.

48. A compound according to claim 1, wherein J is a 3 to 8-membered saturated or unsaturated alkylene chain optionally containing one to two heteroatoms

independently selected from: -O-, -S- or -NR¹²-, wherein R¹² is H, C₁-C₆ alkyl, such as methyl, or -C(=O)C₁-C₆ alkyl, such as acetyl.

49. A compound according to claim 48, wherein J is a 4 to 7-membered saturated or unsaturated, all carbon alkylene chain.

5 50. A compound according to claim 48, wherein J is saturated or mono-unsaturated.

51. A compound according to claim 48, wherein J is dimensioned to provide a macrocycle of 14 or 15 ring atoms.

10 52. A pharmaceutical composition comprising a compound as defined in claim 1, and a pharmaceutically acceptable carrier therefor.

53. A pharmaceutical composition according to claim 52, further comprising an additional HCV antiviral, selected from nucleoside analogue polymerase inhibitors,
15 protease inhibitors, ribavirin and interferon.

54. Use of a compound as defined in claim 1 in therapy.

55. Use of a compound as defined in claim 1 in the manufacture of a medicament
20 for the prophylaxis or treatment of flavivirus infections, including HCV.

56. A method for treatment or prophylaxis of flavivirus infection such as HCV comprising the administration of an effective amount of a compound as defined in claim 1 to an individual afflicted or at risk of such infection.

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